

**No Admission.** The claims presented below are labeled pursuant to the request of the Patent Office for convenience in examination. Reference to a claim as “currently amended” is not an admission that the claim was altered for any reason related to patentability.

1. (currently amended) A binding domain-immunoglobulin fusion protein, comprising:

(a) a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide, wherein said hinge region polypeptide is selected from the group consisting of (i) a mutated hinge region polypeptide that contains one cysteine residue and that is derived from a wild-type immunoglobulin hinge region polypeptide having two or more cysteine residues, (ii) a wild-type human IgA hinge region polypeptide, (iii) a mutated human IgA hinge region polypeptide that contains no cysteine residues and that is derived from a wild-type human IgA hinge region polypeptide, and (iv) a mutated human IgA hinge region polypeptide that contains one cysteine residue and that is derived from a wild-type human IgA hinge region polypeptide;

(b) an immunoglobulin heavy chain CH2 constant region polypeptide that is fused to the hinge region polypeptide; and

(c) an immunoglobulin heavy chain CH3 constant region polypeptide that is fused to the CH2 constant region polypeptide,

wherein:

(1) the binding domain-immunoglobulin fusion protein is capable of at least one immunological activity selected from the group consisting of antibody dependent cell-mediated cytotoxicity and complement fixation, and

(2) the binding domain polypeptide is capable of specifically binding to an antigen.

2. (original) The binding domain-immunoglobulin fusion protein of claim 1 wherein the immunoglobulin hinge region polypeptide is a mutated hinge region polypeptide and exhibits a reduced ability to dimerize, relative to a wild-type human immunoglobulin G hinge region polypeptide.

3. (canceled)

4. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the hinge region polypeptide that contains one cysteine residue is derived from a human IgG1 wild-type hinge region polypeptide.

5. (currently amended) The binding domain Fv-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide comprises:

- (a) at least one immunoglobulin light chain variable region polypeptide;
- (b) at least one immunoglobulin heavy chain variable region polypeptide; and
- (c) at least one linker peptide that is fused to the polypeptide of (a) and to the polypeptide of (b).

6. (currently amended) The binding domain-immunoglobulin fusion protein of claim 5 wherein the immunoglobulin light chain variable region and heavy chain variable region polypeptides are ~~derived from humanized~~immunoglobulins.

7. (currently amended) The binding domain-immunoglobulin fusion protein of claim 1 wherein at least one of the immunoglobulin heavy chain CH2 constant region polypeptide and the immunoglobulin heavy chain CH3 constant region polypeptide are is derived from a human immunoglobulin heavy chain and/or have been altered to be less immunogenic in humans.

8. (original) The binding domain-immunoglobulin fusion protein of claim 1 wherein the immunoglobulin heavy chain constant region CH2 and CH3 polypeptides are of an isotype selected from the group consisting of human IgG and human IgA.

9. (original) The binding domain-immunoglobulin fusion protein of claim 1 wherein the antigen is selected from the group consisting of CD19, CD20, CD37, CD40 and L6.

10. (previously presented) The binding domain-immunoglobulin fusion protein of claim 5 wherein the linker peptide comprises at least one peptide having as an amino acid sequence Gly-Gly-Gly-Gly-Ser.

11. (previously presented) The binding domain-immunoglobulin fusion protein of claim 5 wherein the linker peptide comprises at least three repeats of a peptide having as an amino acid sequence Gly-Gly-Gly-Gly-Ser.

12. (original) The binding domain-immunoglobulin fusion protein of claim 1 wherein the immunoglobulin hinge region polypeptide comprises a human IgA hinge region polypeptide.

13. (original) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide comprises a CD154 extracellular domain.

14-18. (canceled)

19. (original) A pharmaceutical composition comprising a binding domain-immunoglobulin fusion protein according to claim 1 in combination with a physiologically acceptable carrier.

20-22. (canceled)

23. (previously presented) A single chain protein, comprising:

(a) a binding domain polypeptide capable of binding to a target, said binding domain polypeptide being joined to

(b) a hinge peptide, said hinge peptide being joined to

(c) an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to

(d) an immunoglobulin heavy chain CH3 constant region polypeptide,

wherein said hinge peptide is an IgG or IgA hinge peptide that has been made to contain one or two cysteine residues, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted with an amino acid, and

wherein said single chain protein (1) is capable of binding to said target, and (2) is capable of promoting antibody dependent cell-mediated cytotoxicity or complement fixation or both.

24. (previously presented) A single chain protein, comprising:

(a) a binding domain polypeptide capable of binding to a cell surface receptor, said binding domain polypeptide being joined to

(b) a hinge peptide, said hinge peptide being joined to

(c) an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to

(d) an immunoglobulin heavy chain CH3 constant region polypeptide,

wherein said hinge peptide is an IgG or IgA hinge peptide that has been made to contain one or two cysteine residues, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted with an amino acid, and

wherein said single chain protein is capable of antibody dependent cell-mediated cytotoxicity or complement fixation or both.

25. (previously presented) A single chain protein, comprising:
- (a) a binding domain polypeptide capable of binding to a target cell, said binding domain polypeptide being joined to
  - (b) a hinge peptide, said hinge peptide being joined to
  - (c) an immunoglobulin heavy chain CH2 constant region polypeptide, said CH2 constant region polypeptide being joined to
  - (d) an immunoglobulin heavy chain CH3 constant region polypeptide,

wherein said single chain protein is capable of binding to said target and decreasing the number of target cells, and

wherein said hinge peptide is an IgG or IgA hinge peptide that has been made to contain one or two cysteine residues, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted with an amino acid.

26. (previously presented) The single chain protein of any one of claims 23, 24, or 25 wherein said binding domain polypeptide is a single chain Fv polypeptide.

27. (previously presented) The single chain protein of claim 26 wherein said single chain protein is capable of binding to a B cell target.

28. (previously presented) The single chain protein of claim 27 wherein said B cell target is CD20.

29. (previously presented) The single chain protein of claim 27 wherein said B cell target is CD37.

30. (previously presented) The single chain protein of claim 27 wherein said B cell target is selected from the group consisting of CD19, CD22, CD30 ligand, CD54, CD106, and interleukin-12.

31. (previously presented) The single chain protein of claim 27 wherein said single chain protein is capable of depleting a population of target cells.

32. (previously presented) The single chain protein of claim 25 wherein said single chain protein is capable of decreasing the number of target cells in vivo.

33. (previously presented) The single chain protein of claim 25 wherein said single chain protein is capable of decreasing the number of target cells in vitro.

34. (previously presented) The single chain protein of claim 26 wherein the heavy and light chain variable regions of the single chain Fv are joined by a polypeptide linker of at least about 6 amino acids.

35. (currently amended) The single chain protein of claim 25 wherein said binding domain is a single chain Fv polypeptide is capable of binding to a target selected from the group

consisting of CD2, CD5, CD10, CD27, CD28, CD40, CTLA-4, 4-1BB, 4-1BB ligand, interferon- $\gamma$ , interleukin-4, interleukin-17, and interleukin-17 receptor.

36. (currently amended) The single chain protein of claim 25 wherein said binding domain is a single chain Fv polypeptide is capable of binding to a target selected from the group consisting of CD59, CD48, CD72, CD70, CD86/B7.2, CD40 ligand, IL-17, CD43 and VLA-4 ( $\alpha_4\beta_7$ ).

37. (currently amended) The single chain protein of claim 25 wherein said binding domain is a single chain Fv polypeptide is capable of binding to a target selected from the group consisting of CD83 and DEC-205.

38. (currently amended) The single chain protein of claim 25 wherein said binding domain is a single chain Fv polypeptide is capable of binding to a target selected from the group consisting of HER1, HER2, HER3, HER4, epidermal growth factor receptor, vascular endothelial cell growth factor, vascular endothelial cell growth factor receptor, insulin-like growth factor-I, insulin-like growth factor-II, transferrin receptor, estrogen receptor, progesterone receptor, follicle stimulating hormone receptor, retinoic acid receptor, MUC-1, NY-ESO-1, NA 17-A, Melan-A/MART-1, tyrosinase, Gp-100, MAGE, BAGE, GAGE, any of the CTA class of receptors, including in particular the HOM-MEL-40 antigen encoded by the SSX2 gene, carcinoembryonic antigen, and PyLT.

39. (previously presented) The single chain protein of any of claims 23, 24 or 25 wherein said binding domain polypeptide is a single chain Fv capable of binding CD20, wherein said hinge peptide contains one or two cysteines that have been deleted or substituted with non-

cysteine amino acid residues, and wherein said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are IgG1 CH2 and CH3 constant region polypeptides.

40. (previously presented) The single chain protein of claim 39, wherein said single chain protein includes a 2H7 single chain Fv binding domain polypeptide.

41. (previously presented) The single chain protein of claim 39, wherein said single chain protein includes a 2H7 single chain Fv binding domain polypeptide, and wherein said hinge peptide contains one or more serine in place of one or more cysteine residues.

42. (previously presented) The single chain protein of claim 39, wherein wherein said heavy chain constant region comprises a CH2 domain in which a leucine has been replaced with serine at position 234.

43. (previously presented) The single chain protein of claim 42, wherein the binding domain polypeptide is a 2H7 single chain Fv.

44. (previously presented) The protein of claim 5 wherein said binding domain polypeptide is a 2H7 single chain Fv, and wherein said hinge peptide comprises at least a portion of an IgA hinge.

45. (previously presented) The single chain protein of claim 44 wherein said hinge peptide comprises a wild type IgA hinge.

46. (previously presented) The single chain protein of claim 26 wherein said binding domain is a single chain Fv capable of binding a L6 carcinoma antigen, said hinge peptide comprises at least a portion of an IgA hinge, and said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are IgG1 CH2 and CH3 constant region polypeptides.

47. (previously presented) The single chain protein of claim 46 wherein said hinge peptide comprises a wild type IgA hinge.

48. (previously presented) The single chain protein of any of claims 26 wherein said binding domain is an single chain Fv capable of binding a L6 carcinoma antigen, said hinge peptide contains one or two cysteines that have been deleted or substituted with non-cysteine amino acid residues, and said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are IgG1 CH2 and CH3 constant region polypeptides.

49. (previously presented) The single chain protein of claim 1 wherein said hinge peptide (iii) contains three serine residues in place of three cysteine residues.

50. (previously presented) A pharmaceutical composition comprising a protein according to any one of claims 1, 23, 24 or 25, wherein said protein is a single chain protein, in combination with a physiologically acceptable carrier in a form suitable for administration and in an amount useful for the treatment of a malignant condition or B-cell disorder in a patient.

51. (previously presented) A pharmaceutical composition of claim 50 wherein said single chain protein is capable of binding CD20 with a binding affinity of at least about  $10^7 \text{ M}^{-1}$ .

52. (previously presented) A pharmaceutical composition of claim 50 wherein said single chain protein comprises a single chain Fv selected from the group consisting of 2H7 single chain Fvs, L6 single chain Fvs, HD37 single chain Fvs, and G28-1 single chain Fvs.

53. (previously presented) A pharmaceutical composition of claim 50 wherein said single chain protein comprises a single chain Fv capable of binding CD20, wherein said single chain Fv is not a 1F5 single chain Fv.

54. (previously presented) A pharmaceutical composition of claim 52 wherein said single chain Fv is a 2H7 single chain Fv.

55. (previously presented) A pharmaceutical composition of claim 50 wherein said single chain protein comprises a single chain Fv capable of binding to a B cell target.

56. (previously presented) A pharmaceutical composition of claim 55 wherein said B cell target is CD20.

57. (previously presented) A pharmaceutical composition of claim 55 wherein said B cell target is CD37.

58. (previously presented) A pharmaceutical composition of claim 55 wherein said B cell target is selected from the group consisting of CD19, CD22, CD30 ligand, CD54, CD106, and interleukin-12.

59. (previously presented) A pharmaceutical composition of any of claims 51-58 wherein the binding domain polypeptide of said single chain protein comprises a heavy chain variable region and a light chain variable region, wherein said heavy and light chain variable regions of the scFv are joined by a polypeptide linker of at least about 6 amino acids.

60. (previously presented) A pharmaceutical composition of claim 50 wherein the binding domain polypeptide of said single chain protein comprises a single chain Fv polypeptide capable of binding to a target selected from the group consisting of CD2, CD5, CD10, CD27, CD28, CD40, CTLA-4, 4-1BB, 4-1BB ligand, interferon- $\gamma$ , interleukin-4, interleukin-17, and interleukin-17 receptor.

61. (previously presented) A pharmaceutical composition of claim 50 wherein the binding domain polypeptide of said single chain protein comprises a single chain Fv polypeptide capable of binding to a target selected from the group consisting of CD59, CD48, CD72, CD70, CD86/B7.2, CD40 ligand, IL-17, CD43 and VLA-4 ( $\alpha_4\beta_7$ ).

62. (previously presented) A pharmaceutical composition of claim 50 wherein the binding domain polypeptide of said single chain protein comprises a single chain Fv polypeptide capable of binding to a target selected from the group consisting of CD83 and DEC-205.

63. (previously presented) A pharmaceutical composition of claim 50 wherein said binding domain polypeptide of said single chain protein comprises a single chain Fv polypeptide capable of binding to a target selected from the group consisting of HER1, HER2, HER3, HER4, epidermal growth factor receptor, vascular endothelial cell growth factor, vascular endothelial cell growth factor receptor, insulin-like growth factor-I, insulin-like growth factor-II, transferrin receptor, estrogen receptor, progesterone receptor, follicle stimulating hormone receptor, retinoic acid receptor, MUC-1, NY-ESO-1, NA 17-A, Melan-A/MART-1, tyrosinase, Gp-100, MAGE, BAGE, GAGE, any of the CTA class of receptors including in particular HOM-MEL-40 antigen encoded by the SSX2 gene, carcinoembryonic antigen, and PyLT.

64. (previously presented) A pharmaceutical composition of claim 50 wherein said single chain protein comprises a single chain Fv capable of binding to a human CD20, and wherein the hinge peptide of said single chain protein is an altered naturally-occurring immunoglobulin hinge region polypeptide.

65. (previously presented) A pharmaceutical composition of claim 64 wherein said altered naturally-occurring immunoglobulin hinge region polypeptide is an altered IgG1 hinge region polypeptide.

66. (previously presented) A pharmaceutical composition of claim 65 wherein said altered IgG1 hinge region polypeptide is an altered human IgG1 hinge region polypeptide.

67. (previously presented) A pharmaceutical composition of claim 64 wherein said altered naturally-occurring immunoglobulin hinge region polypeptide is an altered IgD hinge region polypeptide.

68. (previously presented) A pharmaceutical composition of claim 64 wherein said altered naturally-occurring immunoglobulin hinge region polypeptide is selected from the group consisting of an altered IgG2 hinge region polypeptide, an altered IgG3 hinge region polypeptide, and an altered IgG4 hinge region polypeptide.

69. (previously presented) A pharmaceutical composition of claim 68 wherein said altered IgG2, IgG3 and IgG4 hinge region polypeptides are altered human IgG2, IgG3 and IgG4 hinge region polypeptides.

70. (previously presented) A pharmaceutical composition of claim 64 wherein said altered naturally-occurring immunoglobulin hinge region polypeptide is an altered IgA hinge region polypeptide.

71. (previously presented) A pharmaceutical composition of claim 70 wherein said altered IgA hinge region polypeptide is an altered human IgA hinge region polypeptide.

72. (previously presented) A pharmaceutical composition of claim 50 wherein the hinge peptide of said single chain protein is mutated naturally-occurring immunoglobulin hinge region polypeptide.

73. (previously presented) A pharmaceutical composition of claim 72 wherein said naturally-occurring immunoglobulin hinge region polypeptide is human.

74. (previously presented) A pharmaceutical composition of claims 72 or 73 wherein said mutated hinge region polypeptide has been altered to contain less cysteine amino acid residues than the naturally-occurring immunoglobulin hinge region polypeptide from which it was derived.

75. (previously presented) A pharmaceutical composition of claims 72 or 73 wherein said mutated immunoglobulin hinge region polypeptide has two cysteine amino acid residues.

76. (previously presented) A pharmaceutical composition of claim 71 wherein said mutated immunoglobulin hinge region polypeptide is an IgG hinge region polypeptide having two cysteine amino acid residues.

77. (previously presented) A pharmaceutical composition of claims 72 or 73 wherein said mutated immunoglobulin hinge region polypeptide has one cysteine amino acid residue.

78. (previously presented) A pharmaceutical composition of claims 72 or 73 wherein said mutated immunoglobulin hinge region polypeptide has no cysteine amino acid residues.

79. (previously presented) A pharmaceutical composition of claim 77 wherein said mutated immunoglobulin hinge region polypeptide is an IgG hinge region polypeptide having one cysteine amino acid residue.

80. (previously presented) A pharmaceutical composition of claim 77 wherein said mutated immunoglobulin hinge region polypeptide is an IgG1 hinge region polypeptide having one cysteine amino acid residue and wherein said cysteine amino acid residue is not the IgG1 hinge region cysteine residue responsible for forming a disulfide bond with a light chain cysteine residue.

81. (previously presented) A pharmaceutical composition of claim 77 wherein said mutated immunoglobulin hinge region polypeptide is an IgA hinge region polypeptide having one cysteine amino acid residue.

82. (previously presented) A pharmaceutical composition of claim 78 wherein said mutated immunoglobulin hinge region polypeptide is an IgG hinge region polypeptide having no cysteine amino acid residues.

83. (previously presented) A pharmaceutical composition of claim 78 wherein said mutated immunoglobulin hinge region polypeptide is an IgA hinge region polypeptide having no cysteine amino acid residues.

84. (previously presented) A pharmaceutical composition of claim 50 wherein the hinge peptide of said single chain protein is selected from the group consisting of naturally occurring immunoglobulin hinge region polypeptides and mutated immunoglobulin hinge region polypeptides.

85. (previously presented) A pharmaceutical composition of claim 84 wherein said hinge peptide is from about 5 to about 65 amino acids.

86. (previously presented) A pharmaceutical composition of claim 84 wherein said hinge peptide is from about 10 to about 50 amino acids.

87. (previously presented) A pharmaceutical composition of claim 84 wherein said hinge peptide is from about 15 to about 35 amino acids.

88. (previously presented) A pharmaceutical composition of claim 84 wherein said hinge peptide is from about 18 to about 32 amino acids.

89. (previously presented) A pharmaceutical composition of claim 84 wherein said hinge peptide is from about 20 to about 30 amino acids.

90. (previously presented) A pharmaceutical composition of any of claims 85-89, wherein said hinge peptide further comprises one or more C-terminal CH1 domain amino acids.

91. (previously presented) A pharmaceutical composition of any of claims 85-89, wherein said hinge peptide further comprises one or more C-terminal CH2 domain amino acids.

92. (previously presented) A pharmaceutical composition of claim 50 wherein said immunoglobulin heavy chain CH2 constant region polypeptide is an IgG heavy chain CH2 constant region polypeptide.

93. (previously presented) A pharmaceutical composition of claim 50 wherein said immunoglobulin heavy chain CH3 constant region polypeptide is an IgG heavy chain CH3 constant region polypeptide.

94. (previously presented) A pharmaceutical composition of claims 92 or 93 wherein said constant region polypeptides are human constant region polypeptides.

95. (previously presented) A pharmaceutical composition of claim 50 wherein said immunoglobulin heavy chain CH2 constant region polypeptide is an IgA heavy chain CH2 constant region polypeptide.

96. (previously presented) A pharmaceutical composition of claim 50 wherein said immunoglobulin heavy chain CH3 constant region polypeptide is an IgA heavy chain CH3 constant region polypeptide.

97. (previously presented) A pharmaceutical composition of claims 95 or 96 wherein said constant region polypeptides are human constant region polypeptides.

98. (currently amended) A pharmaceutical composition of claim 50 wherein said target is CD20 and said binding protein is capable of binding CD20, one or two ~~more~~ cysteine residues in said hinge peptide have been replaced with one or more serine residues, and said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are from IgG1.

99. (previously presented) A pharmaceutical composition of claim 98, wherein said single chain protein is a 2H7 single chain Fv, and one or more cysteine residues in said hinge peptide have been replaced with one or more serine residues.

100. (previously presented) A pharmaceutical composition of claim 50 wherein said target is CD20, said binding domain is capable of binding CD20, one or more cysteine residues in said hinge peptide have been replaced with one or more serine residues, and wherein said heavy chain constant region comprises a CH2 domain where leucine is substituted with serine at position 234.

101. (previously presented) A pharmaceutical composition of claim 99, wherein said single chain protein is a 2H7 scFv in which three cysteine residues in said hinge peptide are substituted with serine.

102. (previously presented) The single chain protein of claim 26 wherein said single chain Fv polypeptide is a 2H7 scFv, wherein said hinge peptide comprises at least a portion of an IgA hinge.

103. (previously presented) The single chain protein of claim 102 wherein said hinge peptide comprises a wild type IgA hinge.

104. (previously presented) The single chain protein of claim 26 wherein said target is an L6 carcinoma antigen, said binding domain is capable of binding L6, said hinge peptide comprises at least a portion of an IgA hinge, and said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are from IgG1.

105. (previously presented) The single chain protein of claim 104 wherein said hinge peptide comprises a wild type IgA hinge.

106. (previously presented) The single chain protein of claim 26 wherein said target is an L6 carcinoma antigen, said binding domain is capable of binding L6, one or more cysteine residues in said hinge peptide have been replaced with one or more serine residues, and said immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are from IgG1.

107. (previously presented) A single chain protein comprising a single chain Fv binding domain polypeptide capable of binding to CD20 joined to an IgE constant hinge region

polypeptide which is joined to an immunoglobulin heavy chain CH2 CH3 constant region polypeptide.

108. (previously presented) A single chain protein of claim 107 wherein said IgE constant hinge region polypeptide is a human IgE constant hinge region polypeptide.

109. (previously presented) A pharmaceutical composition according to claim 50 wherein said malignant condition or a B-cell disorder is selected from the group consisting of rheumatoid arthritis, myasthenia gravis, Grave's disease, type I diabetes mellitus, multiple sclerosis and an autoimmune disease.

110. (previously presented) The binding domain immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide is a single chain Fv.

111. (previously presented) The binding domain immunoglobulin fusion protein of claim 110 wherein said single chain Fv comprises a murine variable light chain and a murine variable heavy chain.

112. (previously presented) The binding domain immunoglobulin fusion protein of claim 110 wherein said single chain Fv comprises a human variable light chain and a human variable heavy chain.

113. (previously presented) The binding domain immunoglobulin fusion protein of claim 110 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

114. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide binds to CD19.

115. (previously presented) The binding domain immunoglobulin fusion protein of claim 114 wherein the binding domain polypeptide is a single chain Fv.

116. (previously presented) The binding domain immunoglobulin fusion protein of claim 115 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

117. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide binds to CD20.

118. (previously presented) The binding domain immunoglobulin fusion protein of claim 117 wherein the binding domain polypeptide is a single chain Fv.

119. (previously presented) The binding domain immunoglobulin fusion protein of claim 118 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

120. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide binds to CD37.

121. (previously presented) The binding domain immunoglobulin fusion protein of claim 120 wherein the binding domain polypeptide is a single chain Fv.

122. (previously presented) The binding domain immunoglobulin fusion protein of claim 121 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

123. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide binds to CD40.

124. (previously presented) The binding domain immunoglobulin fusion protein of claim 123 wherein the binding domain polypeptide is a single chain Fv.

125. (previously presented) The binding domain immunoglobulin fusion protein of claim 124 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

126. (previously presented) The binding domain-immunoglobulin fusion protein of claim 1 wherein the binding domain polypeptide binds to L6.

127. (previously presented) The binding domain immunoglobulin fusion protein of claim 126 wherein the binding domain polypeptide is a single chain Fv.

128. (previously presented) The binding domain immunoglobulin fusion protein of claim 127 wherein said single chain Fv comprises a non-human variable light chain and a non-human variable heavy chain whose sequences have been altered to be less immunogenic in humans.

129. (previously presented) The binding domain immunoglobulin fusion protein of claim 2 wherein said ability to dimerize is evaluated using a biochemical separation technique for resolving proteins on the basis of molecular size and/or a comparison of protein physicochemical properties before and after introduction of a disulfide-reducing agent.

130. (previously presented) The binding domain immunoglobulin fusion protein of claim 6 wherein said immunoglobulin light chain variable region and heavy chain variable region polypeptides are human.

131. (previously presented) The binding domain immunoglobulin fusion protein of claim 6 wherein said immunoglobulin light chain variable region and heavy chain variable region polypeptides are humanized.

132. (previously presented) The binding domain immunoglobulin fusion protein of claim 7 wherein the immunoglobulin heavy chain CH2 and the immunoglobulin heavy chain CH3 constant region polypeptides are human.

133. (previously presented) The binding domain immunoglobulin fusion protein of claim 127 wherein the human immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are human IgG CH2 and CH3 constant region polypeptides.

134. (previously presented) The binding domain immunoglobulin fusion protein of claim 127 wherein the human immunoglobulin heavy chain CH2 and CH3 constant region polypeptides are human IgA CH2 and CH3 constant region polypeptides.

135. (previously presented) A binding domain-immunoglobulin fusion protein according to any one of claims 1, 2, 4-12 or 13, wherein said binding domain-immunoglobulin fusion protein has a  $K_a$  of at least about  $10^7 \text{ M}^{-1}$ .

136. (previously presented) A binding domain-immunoglobulin fusion protein according to any one of 110-135, wherein said binding domain-immunoglobulin fusion protein has a  $K_a$  of at least about  $10^7 \text{ M}^{-1}$ .

137. (previously presented) A pharmaceutical composition comprising a binding domain-immunoglobulin fusion protein according to any one of claims 2, 4-12 or 13 in combination with a physiologically acceptable carrier.

138. (previously presented) A pharmaceutical composition comprising a binding domain-immunoglobulin fusion protein according to any one of claims 110-135 in combination with a physiologically acceptable carrier.

139. (previously presented) The single chain protein of claim 23 wherein said target is a protein.

140. (previously presented) The single chain protein of claim 23 wherein said target is a cell surface receptor.

141. (previously presented) The single chain protein of claim 23 wherein said target is not a cell surface receptor.

142. (previously presented) The single chain protein of claim 39 wherein one or both of said IgG1 CH2 and CH3 constant region polypeptides are human IgG1 CH2 and CH3 constant region polypeptides.

## REMARKS

Applicants wish to thank the Examiner for the granting a telephonic interview on November 16, 2004 with their representatives, Bradford J. Duft of Buchanan Ingersoll and Dr. Judith Woods, Vice President, Legal Affairs and Chief Patent Counsel at Trubion Pharmaceuticals, assignee of the subject application. The substance of the discussion is set forth below as indicated.

The instant Application was filed on January 17, 2002, with 22 claims, four of which are independent (claims 1, 15, 18, and 20). In response to a February 12, 2003 Restriction Requirement, Applicants elected, with traverse, to pursue claims 1-14 and 19 (Group I) in this application.

Claims 1-14 and 19 were rejected in a May 22, 2003 Office Action. Applicants responded on October 22, 2003, arguing against the rejections and adding new claims 23-109. In a subsequent Office Action dated January 2, 2004, a number of the rejections were withdrawn. Applicants responded on June 2, 2004, arguing against the rejections, adding new claims 110-142, and canceling claims 3, 14-18, and 20-22. Claims 1-2, 4-13, 19, and 23-142 are therefore pending.

Four rejections were withdrawn in the Office Action mailed August 27, 2004. The rejection of claims 1, 2, 5, 7-11, 19, 24-28, 31-34, 39, 50-51, 72-74, 84-87, 93-94, and 97 under 35 USC § 102(b) for alleged anticipation by Shan *et al.* was withdrawn (August 27, 2004 Office Action, ¶6). The rejection of claims under 35 USC § 103(a) over Shan *et al.* in further view of Bodmer *et al.* was withdrawn (August 27, 2004 Office Action, ¶7). The rejections of claims 23 and 26-109 under 35 USC § 112, first paragraph was withdrawn (August 27, 2004 Office Action, ¶8). The rejection of claims under 35 USC § 103(a) over Shan *et al.* in view of Kurcherlapati *et al.* was also withdrawn (August 27, 2004 Office Action, ¶9).

In this Response, claims 1, 5, 6, 7, and 35-38 have been amended for reasons set forth below. Entry of these amendments is hereby requested. No new matter has been added.

### **Rejections Maintained**

Five rejections from the January 2, 2004 Office Action were maintained by the Patent Office in the August 27, 2004 Office Action. Each is addressed below.

#### **35 USC § 112, Second Paragraph**

The rejection of claims 1, 2, 4-13, 19, 50-101, and 109-141 under 35 USC § 112, second paragraph, as allegedly “indefinite” with regard to a use of the word “derived” was maintained (August 27, 2004 Office Action, ¶10). This rejection is traversed in its entirety.

The Office Action states “claim 1 for example recites ‘derived from a wild-type human IgA region polypeptide’ wherein the hinge region is not recited as being ‘derived from a wild-type human IgA hinge region’ as argued in the response.” Applicants thanked the Examiner during their telephonic interview for pointing out this typographical error. Claim 1 has been amended solely in order to correct this manifest typographical error by revising, in two places, the phrase “derived from a wild-type human IgA region polypeptide” to --derived from a wild-type human IgA hinge region polypeptide--. Discernable typographical errors cannot support a rejection under 35 USC § 112, second paragraph. No substantive change is intended or made by this correction and the claim has not been amended for any reason related to patentability, as the claims were and are clear both prior to and after this correction.

As noted during the telephonic interview, with regard to claim 6 and the reference to variable region polypeptides, claim 6 has been corrected to replace the statement that the variable regions are “derived from human immunoglobulins” with the statement that they --are humanized --. This correction was not made in response to this rejection. The claim was and is definite both prior to and after this correction, and the claim has not been amended for any

reason related to patentability since the term “derived” is clear and its meaning understandable and unambiguous. Applicants request that the rejection of claim 6 (and dependent claims 130 and 131) be reconsidered and withdrawn.

With regard to claim 7 and the reference to CH2 and CH3 polypeptides, as noted to the Examiner during the telephonic interview, claim 7 has been amended to specify that the CH2 and CH3 polypeptides are either --human and/or have been altered to be less immunogenic in humans--. Again, the claim is not amended in response to this rejection. The claim is not amended for any reason related to patentability, as the claims were and are clear and unambiguous in light of the written description both prior to and after this amendment and the 35 USC § 112, second paragraph rejection is inapposite. Applicants request that the rejection of claim 7 (and dependent claim 132) be reconsidered and withdrawn.

Applicants also request that the rejection of claims 139-141 be reconsidered and withdrawn. Claim 23, from which these claims depend, does not use the term “derived.”

For at least the reasons set forth above, Applicants request that the rejection of claims 1, 2, 4-13, 19, 50-101, and 109-141 under 35 USC § 112, second paragraph, as allegedly “indefinite” be reconsidered and withdrawn.

### **35 USC § 102(b)**

The rejection of claims 78, 82, and 98 under 35 USC § 102(b) as allegedly anticipated by Shan *et al.* was maintained (August 27, 2004 Office Action, ¶11).

As noted to the Examiner during the telephonic interview, in order to expedite prosecution, claims 78 and 82 have been canceled without prejudice in this Response.

Applicants also noted during the interview that, claim 98 contains a typographical error that is clear in view of the claim from which it depends. Claim 98 has been corrected to note that one or two cysteine residues has been substituted, as specified in the claim that it depends from.

A manifest typographical error cannot support a rejection under 35 USC § 112, second paragraph. No substantive change is intended or has been made by this correction, and the claim has not been amended for any reason related to patentability. The claims were and are clear in light of the written description both prior to and after this amendment.

Applicants request that the rejection of claims 78, 82, and 98 under 35 USC § 102(b) be reconsidered and withdrawn.

### **35 USC § 112, First Paragraph**

**Paragraph 12** – In paragraph 12 of the August 27, 2004 Office Action, the rejection of claims 40, 41, 43-48, 52-54, 99, and 101-102 under 35 USC § 112, first paragraph were maintained. The Examiner requested that V<sub>H</sub> and V<sub>L</sub> sequences for various named hybridomas be identified by SEQ ID NO., or the availability of the hybridomas identified by ATCC number. As noted in Applicants' previous Response, and during the telephonic interview, specific binding domains in the rejected claims include those described in the originally filed specification and/or known to those in the art, and the rejection is believed to be inapposite. However, for the convenience of the Examiner, Applicants note the following information (also provided during the telephonic interview).

**2H7** – With respect to claims 40, 41, 43-45, 52-54, 99, 101, and 102, sequences for 2H7 single chain Fv polypeptides are provided in the instant specification and sequence listings. SEQ. ID NO. 11 provides the sequences for 2H7 V<sub>H</sub> and V<sub>L</sub>. These sequences are applicable, for example, to the portion of claim 52 directed to 2H7 single chain Fv polypeptides.

**L6** – With respect to claim 52, L6 sequences are known in the art from U.S. Pat. No. 5,354,847, and the L6 cell line is publicly available from the American Type Culture Collection (ATCC Nos. HB 8677, HB 9240, and HB 9241, as described in US 5,354,847). See also page 36 of Applicants' June 02, 2004 Response.

**HD37** – Light chain variable domain and heavy chain variable domain sequences for HD37 are provided in SEQ ID NO:8.

**G28.1** – Light chain variable domain and heavy chain variable domain sequences for G28-1 are provided in SEQ ID NO:13.

**1F5** – Light chain variable domain and heavy chain variable domain sequences for 1F5 were deposited in GenBank and the accession numbers are AY058907 for V<sub>H</sub> and AY058906 for V<sub>L</sub>. The V<sub>H</sub> and V<sub>L</sub> sequences are also set forth in Figure 3 of Shan *et al.*, *Blood* **91**: 1644-1652 (1998), and the 1F5 hybridoma is deposited with the American Type Culture Collection (ATCC No. HB-9645).

Applicants request that this rejection be reconsidered and withdrawn.

**Paragraph 13** – In paragraph 13 of the August 27, 2004 Office Action, the rejection of claim 53 was maintained. Claim 53 specifies that the single chain protein includes a single chain Fv that is not a 1F5 single chain Fv. The Examiner asserted that In re Johnson is not applicable to the instant claims.

As noted to the Examiner during the telephonic interview, Section 2173.05 of the MPEP cites In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187 (CCPA 1977), and specifically provides that, “If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.” That is the case here.

The *Johnson* court held that “[t]he notion that one who fully discloses, and teaches those skilled in the art how to make and use a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.” *Id.* The Examiner appears to view *Johnson* as inapplicable based on the number of the

species listed in the patent. However, neither the MPEP nor the Johnson case includes such a restriction. In fact, the Johnson court stated, “the written description in the [] specification supported the claims in the absence of the limitation, and that specification, having described the whole, necessarily described the part remaining.” *Id.* Thus, there is no numerical minimum required to apply this case, so long as there is adequate disclosure for the genus, which the PTO has already agreed there to be, and Applicants respectfully request that this rejection be reconsidered and withdrawn.

**Paragraph 14** – In paragraph 14 of the August 27, 2004 Office Action, the rejection of claims 107 and 108 was maintained. With regard to recitation of an IgE hinge region polypeptide, the Patent Office asserts a lack of support “for the limitation of an IgE hinge.” In response to Applicants’ argument, Examiner stated, “The analysis is compared to a claim of a specific protein and the specification has a statement that “any protein can be used in the invention.”

Applicants respectfully disagree. As emphasized during the telephonic interview, the specification does not state, nor did Applicants, that “any protein can be used.” To the contrary, in specific reference to the hinge region, the “Detailed Description of the Invention” at page 22 of the specification teaches:

An immunoglobulin hinge region polypeptide, as discussed above, includes any hinge peptide or polypeptide that occurs naturally, as an artificial peptide or as the result of genetic engineering and that is situated in an immunoglobulin heavy chain polypeptide between the amino acid residues responsible for forming intrachain immunoglobulin-domain disulfide bonds in CH1 and CH2 regions; hinge region polypeptides for use in the present invention may also include a mutated hinge region polypeptide.

It is well settled that the PTO has the burden of making out a *prima facie* case that the rejected claims do not comply with § 112, first paragraph, written description requirement, by setting forth evidence or reasons why, as a matter of fact, the written description in a disclosure

would not reasonably convey to persons skilled in this art that appellant was in possession of the invention defined by the claims, including all of the limitations thereof, at the time the application was filed. *See generally, In re Alton*, 76 F.3d 1168, 1172, 1175-76, 37 USPQ2d 1578, 1581, 1583-84 (Fed. Cir. 1996). It is further well settled that the written description does not have to describe the invention later claimed *in haec verba*. The written description need only “convey with reasonable clarity to those skilled in the art that . . . applicant was in possession of the invention . . . now claimed.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991); *see also Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *In re Wertheim*, 541 F.2d 257, 262-65, 191 USPQ 90, 96-98 (CCPA 1976). Thus, where “the specification contains a description of the claimed invention, albeit not *in ipsius verbis* (in the identical words), then the Examiner, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient.” *Alton* 76 F.3d at 1175-76, 37 USPQ2d at 1583.

Here, it cannot be gainsaid that the various naturally occurring hinge peptides are known to include IgE immunoglobulin hinge regions, and the Examiner has not provided evidence or reasoning why the description of an “immunoglobulin hinge region polypeptide” by reference “any hinge peptide or polypeptide that occurs naturally” would not be understood by those in the art to include an IgE hinge region polypeptide.

Applicants request that the 35 USC § 112, first paragraph, rejections of claims 107 and 108 be reconsidered and withdrawn.

### **New Grounds of Rejection**

#### **35 USC § 112, Second Paragraph**

Claims 1, 2, 4-13, 19, and 23-142 were rejected under 35 USC § 112, second paragraph. This rejection is traversed and reconsideration and withdrawal is respectfully requested.

a. In questioning whether claims 1, 23, 24, and 25 are definite, the Patent Office asks, “are the binding domain polypeptide or the single chain protein joined directly to the hinge or can some peptide or amino acid residue be in between as a linker?” (August 27, 2004 Office Action, ¶15, subpart A). The Office Action further states that claim 1 could be interpreted as being directed to “a binding domain fused to a hinge with a CH1 domain fused to a hinge with the heavy chain fused to the CH1 and the heavy chain is part of a binding domain.” Applicants respectfully traverse the rejection in its entirety.

Claim 1 reads, in part, “a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide.” Claims 23-25 read, in part, a “binding domain polypeptide being joined to (b) a hinge peptide.” Each of the claims recite that the binding domain is fused or joined to a hinge. The language of the claims is clear. The recited portions of the claimed proteins may be directly adjacent one another, and various embodiments in the specification exemplify this. It is noted at page 29 of the Specification, for example, that in “preferred embodiments the CH1 domain is deleted and the carboxyl end of the second variable region is joined to the amino terminus of CH2 through the hinge region,” and such constructs are described in various examples.

The claims are not unclear under the law simply because they may be indirectly joined. Furthermore, as with any claim to a protein or polypeptide having a certain structure, it is understood that alterations may be made that do not destroy function. Thus, where function is not eliminated, here where the claimed protein is capable of binding its target and promoting antibody dependent cell-mediated cytotoxicity and/or complement fixation as set forth, those in the art may determine that the recited portions of the claimed proteins may be indirectly joined.

The second paragraph of 35 USC §112 requires that a specification include claims “particularly pointing out and distinctly claiming the subject matter which the applicant regards

as his invention.” Indefiniteness is a question of law, Carl Zeiss Stiftung v. Renishaw PLC, 945 F.2d 1173, 1181, 20 USPQ2d 1094, 1101 (Fed. Cir. 1991), and determining whether a claim is indefinite requires an analysis of “whether one skilled in the art would understand the bounds of the claim when read in light of the specification . . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more.” Miles Lab., Inc. v. Shandon Inc., 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994); *see also* Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). So it is with the instant case. Given the teachings of the specification, including the original claims, it is plain that – as the Examiner himself did – one of ordinary skill in the art would readily understand the metes and bounds of what applicant has claimed as his invention.

As noted in In re Borkowski, 442 F.2d 904, 909, 164 USPQ 642, 645-46 (CCPA 1970): “The first sentence of the second paragraph of §112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention” (footnotes omitted, emphasis in original). *Accord* Exxon Research and Engineering Co. v. U.S., 60 USPQ2d 1272 (2001) (“If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2.”). Here, it is plain that the claims are not indefinite under the law, and Applicants respectfully request that the rejection of claims 1 and 23-25, under 35 USC § 112, second paragraph, and all rejected claims that depend from them, be reconsidered and withdrawn.

b. The Office Action alleges that there is insufficient antecedent basis for the use of “said single chain Fv” in claims 35-38. Applicants thanked the Examiner during the telephonic interview for pointing this out this typographical error. Although it in no way impacts patentability of the invention, and can form no substantive basis for a rejection of claims, which is traversed in its entirety, claims 35-38 have been corrected to fix this typographical error. A manifest typographical error can never support a rejection of claims under 35 USC § 112, second paragraph. As is plain from the correction of the claims, no subject matter has been deleted or altered in scope, and the claims were and are clear and definite, and Applicants request that the rejection of claim 35-38 under 35 USC § 112, second paragraph be reconsidered and withdrawn.

c. The Office Action alleges that there is insufficient antecedent basis for the use of the phrase “binding domain Fv-immunoglobulin fusion protein” in claim 5. Applicants also thanked the Examiner during the telephonic interview for pointing this out this typographical error. Although it in no way impacts patentability of the invention, and can form no substantive basis for a rejection of this claim, which is traversed in its entirety, claim 5 has been corrected to fix this typographical error. As is plain from the correction of the claim, no subject matter has been deleted or altered in scope, and the claims were and are clear and definite. Applicants respectfully request that the rejection of claim 5 under 35 USC § 112, first paragraph, and all rejected claims that depend from it, be reconsidered and withdrawn.

### **35 USC § 102(b)**

Claims 1, 2, 4, 7, 8, 19, and 135-138 were rejected under 35 USC § 102(b) as allegedly anticipated by Bodmer *et al.* The Office Action asserts that, because of the alleged “indefinite nature of claim 1,” the claim is interpreted as a binding domain fused to a hinge with a CH1 domain fused to a hinge with the heavy chain fused to the CH1 and the heavy chain is part of a binding domain.” As noted above and during the telephonic interview with the Examiner, the

Bodmer *et al.* patent is directed to complete antibodies and (Fab')<sub>2</sub> fragments. Bodmer *et al.* does not teach the claimed binding domain-immunoglobulin fusion protein having a binding domain polypeptide coupled to one of hinge molecules (i) - (iv) coupled to CH<sub>2</sub>CH<sub>3</sub>, either directly or indirectly, with or without a CH<sub>1</sub> domain. Bodmer *et al.* also fails to teach or suggest a protein or polypeptide lacking a CH<sub>1</sub> domain (see, for example, Applicants' specification at page 29) and, indeed, makes repeated reference to a molecule that includes a CH<sub>1</sub> region (see, for example, column 3, lines 13-17; column 3, lines 46-50; column 4, lines 28-35; column 6, lines 52-56; column 8, lines 1-3; column 8, lines 26-34). That Bodmer *et al.* does not anticipate the claimed inventions is also clear from the assertion in the Office Action at page 8 that Bodmer *et al.* appear to have "produced antibodies that are identical to the claimed antibody" (emphasis added). Applicants have not claimed an "antibody" as that term is used in Bodmer *et al.* and understood in the art, *i.e.*, a four-chain Ig molecule. Bodmer *et al.* refers to antibodies as "natural immunoglobulins" comprising "a generally Y-shaped molecule," and as "having full length heavy and light chains."

The rejection under 35 USC § 102(b) as allegedly anticipated by Bodmer *et al.* cannot stand and Applicants respectfully request that it be reconsidered and withdrawn.

### **35 USC § 102(e)**

Claims 1, 2, 4, 5, 6-8, 12, 19, 110, 129, 135-138 were rejected under 35 USC § 102(e) as allegedly anticipated by Gillies *et al.* (U.S. 2003/0044423A1, hereinafter the "Gillies Published Application," which claims priority to U.S. Ser. No. 60/274,096, hereinafter the "Gillies Provisional"). The following was noted to the Examiner during the telephonic interview.

Neither the Gillies Provisional nor the Gillies Published Application is directed to constructs such as those claimed in the instant application, and there is no anticipation. Additionally, much of the information in the Gillies Published Application (including six of the

eleven paragraphs cited by the Patent Office) is not found in the Gillies Provisional and thus cannot be prior art because it first appears in an application filed subsequent to the instant application.

*The Gillies Provisional* – The March 7, 2001 Gillies Provisional is for “Expression Technology for Fusion Proteins Containing an Antibody Moiety” (emphasis added). On pages 1 and 2, the Gillies Provisional recites concerns over the efficiency of protein expression, expression of proteins in proper conformation, and the expression of proteins that are substantially non-aggregated. In particular, it professes to describe “the production of antibody and antibody fusion protein preparations with reduced aggregation” (page 2; emphasis added).

At page 3, the “Summary of the Invention” refers to “methods and compositions useful for producing intact antibodies, immunocytokines, immunofusions, immunoligands, and other antibody and Fc fusion proteins that enhance the expression, proper oligomerization and purification of a desired fusion protein preferably with decreased Fc effector functions” (emphasis added). Preferred embodiments are said to include modified and chimeric whole antibodies, for example, “an IgG2, modified to contain fewer disulfide bonds in the hinge region, or an IgG2 CH2 and CH3 region in which the hinge region derives from another antibody, preferably a normal or mutant IgG1 hinge region.” Such molecules are depicted in Figure 1, the only Figure in the application, which shows whole antibodies in the typical four-chain configuration (see also the “Brief Description of the Drawings” at page 8).

Non-immunoglobulin components of the fusion molecules are said to include proteins, hormones, cytokines, and ligand-binding proteins (pages 4-5) and, as noted above, preferred molecules have “reduced effector functions” (page 5, 2nd paragraph).

*The Gillies et al. Published Application* – The March 7, 2002 Gillies Published Application (“Expression Technology for Proteins Containing a Hybrid Antibody Moiety”; emphasis added) has a title different from the Gillies Provisional. It also adds twelve new claims, three new Figures, six new Examples, and 133 wholly new paragraphs into the written description. Because Applicants’ patent application was filed before March 7, 2002, none of this new subject matter can be used in determining the patentability of any pending claims.

The Patent Office, however, has apparently afforded the Gillies Published Application an effective date of March 7, 2001, the date the Gillies Provisional was filed. But because the Gillies Published Application differs from the provisional it can only claim priority to March 7, 2001 under 35 USC § 102(e), if at all, for disclosure that is also present in the original Gillies Provisional. The 102(e) effective date of the Gillies Published Application for subject matter not present in the provisional patent application is not March 7, 2001, but March 7, 2002, which is after the filing date of the instant application and, thus, cannot be used for the rejection of claims.

In support of the § 102(e) rejection, the Patent Office cited eleven paragraphs from the Gillies Published Application, namely, paragraphs [0015], [0022], and [0026] - [0034]. However, only five of those paragraphs – numbers [0015], [0028], and [0030] - [0032] – are found in the Gillies Provisional. The remaining six paragraphs are present only in the published version of the application. They are thus not entitled to the claimed priority date and cannot be prior art to the instant application for any purpose because the instant application was filed January 17, 2002, and thus predates all subject matter first presented in the Gillies Published Application.

Despite this, the Patent Office alleged that “Gillies et al teach fusion protein of binding molecules fused to the hinge and the hinge can be modified to have only one cysteine or be from an IgG1 or IgA and the CH2 and CH3 are human and the binding domain can be a single chain

Fv or a binding molecule (see Figure 2A, paragraph 0015, 0022, 0026-0034).” Each of these eleven paragraphs is discussed below.<sup>1</sup>

Paragraph [0015] of the Gillies Published Application does not support the Patent Office’s 35 USC § 102(e) rejection. It reads as follows:

[0015] In another set of preferred embodiments, a mutation in the hinge region is also present. For example, in cases where an antibody light chain is also present, a form of an IgG1 hinge region with the cysteine residues in the normal number at their normal positions is preferred. However, in cases where an antibody light chain is not present as a distinct polypeptide chain, an IgG1 hinge in which the first cysteine is mutated to another residue is preferred. For example, it is useful to employ such a mutated hinge region in Fc-X proteins, X-Fc proteins, and in single-chain antibodies in which the light chain variable region is attached to the heavy chain by means of a polypeptide linker. The first cysteine in the IgG1 hinge is preferably mutated to a serine in this context [emphasis added].

The above paragraph refers to an IgG1 hinge with two cysteine residues. It does not teach a molecule where “the hinge can be modified to have only one cysteine,” as asserted by the Patent Office, and paragraph [0015] cannot support a rejection of any of claims 1, 2, 4, 5, 6-8, 12, 19, 110, 129, or 135-138 under 35 USC § 102(e). Anticipation requires identity of invention, and it is plain that neither the Gillies Provisional nor its paragraph [0015] teaches Applicants’ invention.

The Patent Office also refers to paragraphs [0022] and [0026]-[0034] in the Gillies Published Application as support for the § 102(e) rejection. However, and notwithstanding that paragraphs [0022], [0026], [0027], [0029], [0033] and [0034] are not prior art and cannot be used to reject Applicants’ claims, it is equally plain that none of these paragraphs can support the rejection. Paragraphs [0026] - [0031], [0033] and [0034] merely discuss possible “non-Ig moieties”. Furthermore,

- none of the ten numbered paragraphs [0022] or [0026] - [0034] contain any reference to a single chain Fv;

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<sup>1</sup> In making this rejection, the Patent Office also refers to Figure 2A, but the Gillies Provisional does not have a Figure 2 and may thus not be relied on.

- none of the eight numbered paragraphs [0026] - [0031], [0033] or [0034] contain any reference to an immunoglobulin hinge; and,
- none of the eight numbered paragraphs [0026] - [0031], [0033] or [0034] contain any reference to cysteine residues.

In sum, it is plain that none of paragraphs [0026] - [0031], [0033] or [0034] contain reference to any subject matter that could support a § 102(e) rejection of any of claims 1, 2, 4, 5, 6-8, 12, 19, 110, 129, or 135-138. There is no identity of invention as required to establish anticipation.

The only paragraphs cited by the Patent Office that contain any reference to a hinge are paragraphs [0022] and [0032]. Paragraph [0022] is not contained in the Gillies Provisional and is thus not prior art. It does not, in any event, contain any reference to any construct within Applicants' claims. Referring only to the drug Enbrel "in the format TNFR-hinge-CH2-CH3," paragraph [0032] contains one sentence regarding a hinge:

In an alternative preferred embodiment, the non-immunoglobulin component of the fusion protein is a ligand-binding protein with biological activity. Such ligand-binding proteins may, for example, (1) block receptor-ligand interactions at the cell surface; or (2) neutralize the biological activity of a molecule (e.g., a cytokine) in the fluid phase of the blood, thereby preventing it from reaching its cellular target. Preferred ligand-binding proteins include CD4, CTLA-4, TNF receptors, or interleukin receptors such as the IL-1 and IL-4 receptors. Preferably, the antibody-receptor fusion protein of the present invention displays the biological activity of the ligand-binding protein. One highly preferred embodiment comprises the extracellular TNF-receptor domain fragment used in the protein drug Enbrel, in the format TNFR-hinge-CH2-CH3 or hinge-CH2-CH3-TNFR, in which the CH2 and CH3 domains are derived from IgG2 or IgG4 and each of the two hinge regions in the dimeric Fc has three or fewer cysteines, and even more preferably, two or fewer cysteines [emphasis added].

Again, identity of invention cannot be found. Independent claim 1 (from which the remaining rejected claims all depend) specifies, "the binding domain-immunoglobulin fusion protein is capable of at least one immunological activity selected from the group consisting of antibody dependent cell-mediated cytotoxicity and complement fixation." Enbrel, however, is understood

not to mediate ADCC or complement fixation. As noted in FDA approval documents, for example,

The Fc portion of [Enbrel] is not likely to participate in determining the pharmacological activity of the fusion protein. Although biologically active, the Fc portion's effects are inhibited by the far greater concentration of IgG molecules normally found in vivo. The fusion protein was found to be negative in a direct complement-mediated cytotoxicity and complement fixation assay [FDA Clinical Review (October 28, 1998); emphasis added].

See also Barone D, Krantz C, Lambert D, Maggiora K, Mohler K, "Comparative analysis of the ability of etanercept and infliximab to lyse TNF-expressing cells in a complement dependent fashion" [abstract]. *Arthritis Rheum* 42(suppl):S90 (1999) ("Etanercept [Enbrel] did not kill cells in a complement-dependent fashion").

For at least the reasons set forth above, Applicants respectfully request that the rejection of claims 1, 2, 4, 5, 6-8, 12, 19, 110, 129, 135-138 under 35 USC § 102(e) be reconsidered and withdrawn.

### **35 USC § 103**

Claims 1, 2, 4, 5, 6-12, 19, 50, 51, 55, 56, 59, 64-66, 72-79, 82, 84-98, 109-113, 117-119, and 129-138 were rejected under 35 USC § 103(a) as allegedly unpatentable over Gillies *et al.* and further in view of Shan *et al.* and Bodmer *et al.*

The Office Action acknowledges, "Gillies et al does not teach a single chain binding to CD20 or a humanized VH and VL." The Office Action proposes, however, that "These deficiencies are made up for in the teachings of Shan et al and Bodmer et al," and concludes that, "It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used an antibody to CD20 and humanize it in view of Gillies et al, Shan et al, and Bodmer et al." This rejection is respectfully traversed.

Applicants note that, even were these documents combined, which they cannot be, the claimed invention is not arrived at. Thus, the rejection is inapt.

Referring only to the material in the Gillies Provisional (given that the added subject matter in the Gillies Published Application cannot be prior art) it is plain that the Gillies Provisional fails to teach or suggest a hinge that is modified to have only one cysteine. The Gillies Provisional also fails to describe a binding domain fusion protein having a binding domain polypeptide joined to an IgA wild type hinge or an IgA hinge having no cysteines that is joined to immunoglobulin CH2 region constant chain region polypeptide, which is fused to a immunoglobulin CH3 region constant chain region polypeptide. The disclosure of the Gillies Provisional fails to support a rejection of claim 1 under 35 USC § 103(a).

Further, one of ordinary skill in the art would not have been motivated to modify Gillies or combine it with either, or both, of the other documents cited by the Patent Office. Claim 1 of the instant application recites a binding domain-immunoglobulin fusion protein that “is capable of at least one immunological activity selected from the group consisting of antibody dependent cell-mediated cytotoxicity and complement fixation” (emphasis added). The only binding-hinge-CH2CH3 construct disclosed by Gillies is the marketed drug “Enbrel” and, as indicated above, it is not known to have either of the effector function(s) recited in the rejected claims.

Indeed, Gillies appears directed largely to attempts to make molecules with increased expression and greater stability at the expense of effector functions. For example, paragraph [0012] of the Gillies Published Application states, “In one set of preferred embodiments, the invention provides fusion proteins with decreased effector functions and improved assembly. Such fusion proteins are particularly useful when the Ig moiety serves to enhance expression and improve serum half-life, but when the immunological functions of the Ig moiety are not needed” (emphasis added). One way a reduced effector function is achieved in Gillies is by making constructs that do not use CH2 and CH3 domains. Gillies also indicates a preference to ablate effector function. See, for example, the statement in paragraph [0014] that, “In a more preferred

embodiment, the fusion proteins also contain one or more mutations in the Ig moiety. For example, the Ig moiety is mutated to further reduce any remaining effector function that is not desired” (emphasis added).

There is no motivation to combine Gillies with Shan *et al.* Gillies contains no discussion or suggestion regarding a single chain Fv construct that is capable of binding CD20. As discussed in Applicants’ Response filed October 22, 2003, the focus of the Shan *et al.* publication is identified in its title, “Characterization of scFv-Ig Constructs Generated from the Anti-CD20 mAb 1F5 Using Linker Peptides of Varying Lengths” (emphasis added). Shan *et al.* reports the construction of four scFv constructs using nucleic acid constructs encoding the heavy and light chain variable regions from a murine anti-human CD20 monoclonal antibody called 1F5. Each of the scFv constructs was joined to a derivative of human IgG1 (hinge plus CH2 plus CH3) solely “to facilitate purification using staphylococcal protein A” (Abstract, Shan *et al.*). The hinge in Shan *et al.* is derived from IgG1 but has three serine residues included in place of the three cysteine residues normally present in the IgG1 hinge (Methods and Materials, Shan *et al.*). Shan *et al.* fails to teach or suggest any other hinge. There is no discussion in Shan *et al.* regarding a desire to modify the hinge region to have cysteine residues for any purpose.

Likewise, there is no motivation to combine the work of Gillies *et al.* and/or Shan *et al.* with that of Bodmer *et al.*, which relates to whole antibodies and antibody fragments. Bodmer *et al.* states that reduction of the number of cysteines to one “will facilitate assembly of the antibody molecules, particularly bispecific antibody molecules and antibody molecules wherein the Fc portion has been replaced by an effector or reporter molecule, since it will only be necessary to form a single disulfide bond” (col. 3, lines 60-66, emphasis added). As discussed in Applicant’s October 22, 2003 Response, Bodmer *et al.* is directed to use of a single cysteine to

prevent mismatching when constructing a bi-specific antibody or one that would have no ADCC or complement fixation effector function at all, *i.e.*, a molecule that has no Fc region.

These three documents cited by the Patent Office are far afield from each other, and widely disparate.

“To establish a *prima facie* case, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference or references, when combined, must teach or suggest all the claim limitations. MPEP 706.02(j), citing, In re Vaeck, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added).

Gillies *et al.*, Shan *et al.* and Bodmer *et al.* are contrasting and incongruent and there is no basis to combine them. The first is directed to modified antibodies and hybrid antibody fusion proteins said to be expressed at high levels. The second is directed to linker lengths between the V<sub>H</sub> and V<sub>L</sub> in an scFv peptide having an antigen-binding site and no hinge cysteines. The third is fundamentally directed to altered antibody and (Fab')<sub>2</sub> molecules having two antigen binding sites and an increased or decreased number of hinge cysteines “capable of forming a heavy chain to heavy chain disulfide bond” said to be useful for constructing bi-specific antibody and (Fab')<sub>2</sub> molecules or molecules that have no effector function. One of skill in the art would not be motivated to combine the three documents in an effort to produce the instant claimed molecules having the ability to mediate ADCC and/or complement fixation.

The combination of Gillies *et al.*, Shan *et al.* and Bodmer *et al.* does not result in the claimed invention. Nevertheless, it appears as though the Patent Office has used illicit hindsight in an effort to reconstruct the claimed invention. As is well know, however, obviousness cannot be established by hindsight combination. In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885,

1888 (Fed. Cir. 1991). As discussed in Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the alleged prior art itself, and not applicant's achievement, which must establish the obviousness of the combination at the time it was made. W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). It has been held that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine any alleged prior art references.

Applicants respectfully request that the rejection under 35 USC § 103(a) be reconsidered and withdrawn.